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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Oily Solutions for Parenteral Administration containing Adreno-Cortical Hormones

We, FRANCESCO VISMARA, S.p.A., an Italian Body Corporate, of Casatenovo, Como, Italy, and ALBERTO ERCOLI, an Italian Citizen, of Via Circo 12, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with improvements in or relating to pharmaceutical compositions, more particularly with oily solutions for parenteral administration of adreno-cortical hormones.

The preparation of oily solutions of cortical hormones, such as cortisone and hydrocortisone, or of their corresponding Δ^1-dehydro-derivatives, 9-halogen and/or 6-methyl-derivatives, in sufficiently high concentrations required for many therapeutic purposes has been a problem.

It is well known, in fact, that these hormones, as well as their esters which may be used in therapy, are very sparingly soluble in the oily solvents which are commonly employed as vehicles for parenteral use e.g. olive oil, cottonseed oil, sesame oil, arachis oil or ethyl oleate. For this reason these hormones are usually administered parenterally in aqueous suspension or orally. Both these forms of administration have shown, however, a number of significant disadvantages.

Aqueous suspensions are not always well tolerated. The crystalline deposit is usually absorbed from the site of the injection at too slow a rate. The poor absorption may cause phenomena of local intolerance. Aqueous suspensions may also give rise, especially in prolonged treatments, to irritations at the site of injection, which sometimes form abscesses.

Oral administration does not always assure regularity as well as constancy of action, and does not guarantee a complete uptake of the drug. Furthermore prolonged administration of anti-inflammatory hormones by oral route frequently causes gastritis which may complicate into ulcers which are particularly dangerous because of their silentness.

An object of the present invention is to provide compositions of adreno-cortical hormones in the form of oily solutions, in order to reduce the disadvantages of the two above-mentioned forms of administration.

Another object of the invention is to provide oily solutions with a high hormonal concentration which are of considerable importance in the treatment of certain diseases such as leukemia, where high doses of the hormone are required.

It has now been found that very satisfactory parenterally acceptable solutions of adreno-cortical hormones may be prepared by using esters of ricinoleic acid with certain mono and polyhydric alcohols as solvents; such solutions may of course contain other adjuvants which are not esters but which are parenterally acceptable and pharmaceutically compatible therewith such as antioxidants, wetting and dispersing agents and the like.

According to the present invention there is provided an oily composition adapted for parenteral administration comprising an adreno-cortical hormone in solution in a liquid vehicle consisting of a parenterally acceptable ester of ricinoleic acid with a monohydric or polyhydric alcohol containing two or three carbon atoms per molecule with or without other parenterally acceptable compatible adjuvants which are not esters.

By the term "adreno-cortical hormone" is to be understood steroid compounds having adreno-cortical activity. Such compounds include not only those present in nature but also related compounds which are believed not to be present in nature but which have similar activity to a greater or lesser degree. Thus in addition to including naturally-occurring compounds such as cortisone and hydrocortisone it includes derivatives thereof such as prednisone and prednisolone. Moreover, the term also

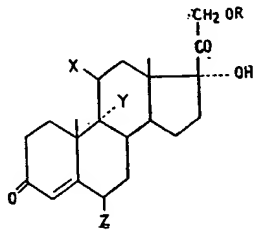
[*Price 3s. 6d.*]

includes 21-esters of any naturally occurring or synthetic adreno-cortical hormones.

Esters of ricinoleic acid with glycerol, propylene glycol or ethyl alcohol are preferred because of their high solubilizing power and of their good local tolerance.

The oily solutions according to the invention are well-tolerated, well-absorbed at the site of injection and accompanied by relatively few side-effects, even in cases where high doses are administered. They possess a high therapeutic value which makes them active at small doses not otherwise effective, as, for instance, in the liver glycogen deposition test where, at equal doses, prednisone in an oily solution has been shown to have an activity five times higher than that of the oral form, (that is in order to obtain the same increase in liver glycogen, an oral dose five times higher than that administered parenterally in oily form must be given).

Although the adreno-cortical hormone used in the oily composition according to the invention may be any desired such compound it is preferred to use a compound of the general formula: —



where

X is ketonic oxygen or a hydroxyl group,
Y is a hydrogen or a halogen atom,
Z is a hydrogen atom or a methyl group and
R is hydrogen or an acyl group or a Δ^1 or a $\Delta^{1:4}$-dehydro-derivative thereof.

If desired, one may use mixtures of adreno-cortical hormones.

It is preferred that the oily compositions according to the invention should contain the adreno-cortical hormone in an amount from 0.1 to 5% by weight of the liquid vehicle.

The vehicles used in the composition according to the invention can be used either individually or in admixture with other such vehicles in various proportions. These vehicles can also be diluted if desired with a further ester component consisting of a parenterally acceptable ester of an alcohol with a carboxylic acid other than ricinoleic acid, said ester containing at least six carbon atoms per molecule, such as olive oil, sesame oil, ethyl oleate, or benzyl benzoate.

The mixtures, for example with ethyl oleate, have a solubilising power inferior to that of pure ricinoleates; on the other hand, they have the advantage of a lower viscosity, so that injection becomes easier.

Tables 1 and 2 show the solubilities of cortisone, prednisone and prednisolone and of some of their esters in the ricinoleic acid esters as compared with their respective solubilities in olive oil or sesame oil.

TABLE 1

	Cortisone acetate mg/cc	Cortisone trimethyl-acetate mg/cc	Cortisone oenanthate mg/cc	Cortisone cyclopentyl-propionate mg/cc	Cortisone phenyl-propionate mg/cc
Olive oil	0.1	0.1	8	3	3
Glyceryl ricinoleate	5	3	60	40	30
Ethyl ricinoleate	3		60	40	26
Glyceryl ricinoleate + Ethyl ricinoleate		2.5 b		40 a	
Glyceryl ricinoleate + Ethyl oleate 1:1	4	2.5	50	30	25

a) = Glyceryl ricinoleate : ethyl ricinoleate = 1 : 1

b) = Glyceryl ricinoleate : ethyl ricinoleate = 1 : 2

TABLE 2

	Prednisone mg/cc	Prednisone acetate mg/cc	Prednisone trimethyl-acetate mg/cc	Prednisone oenanthate mg/cc	Prednisone cyclopentyl-propionate mg/cc	Prednisolone mg/cc	Prednisolone oenanthate mg/cc
Sesame oil	2	2	1	3	2	1	6
Glyceryl ricinoleate	12	10	8	12	10	25	60
Ethyl ricinoleate	10		7			20	40
Glyceryl ricinoleate + Ethyl ricinoleate	8	9	4	10	10		32
Glyceryl ricinoleate + Ethyl oleate 1:1		— 7	3.8	9	8	16	

The adreno-cortical hormones can be dissolved in the ricinoleic acid esters alone or in admixture with other esters in various proportions as stated above. Moreover different esters of the same hormone or various esters of different hormones can be dissolved simultaneously in the same vehicle or in a mixture of different vehicles. By a suitable mixture of a number of esters of the same hormone or of different hormones, oily compositions can be obtained with a high hormonal concentration.

The solutions thus obtained show a substantially normal viscosity after the addition of stabilisers, such as, for example, propyleneglycol or benzyl alcohol and they are practically stable and more advantageous and effective than the aqueous suspensions previously proposed and also than oral therapy. They ensure, in fact, a higher constancy of action with more marked effects and a greater uptake of the drug.

Therapy with such oily solutions has given very favourable results. The oily compositions of the cortical hormones and, particularly, those of the anti-inflammatory hormones, have been found to possess a generally superior therapeutic value to that obtained by aqueous suspensions or by the oral route.

In most conditions of acute and chronic articular rheumatism, infectious diseases, allergic syndromes etc., injectable preparations have been found to give optimal clinical remissions with doses lower than those normally required by the oral route; for example: 15 mgms. of prednisone in oily solution have given results comparable with those obtainable with 20—25 mgms. of the same hormone administered by the oral route. This constitutes an appreciable advantage, even from the economic point of view.

The efficacy of the oily solutions can also be shown by the results obtained in the palliative treatments of certain types of neoplastic diseases, which results are quite as encouraging as they are unexpected. The oily solutions of the cortical hormones have proved to be particularly useful in giving some measure of relief in cases of pulmonary carcinoma, prostatic cancer, breast cancer and, though less frequently, in uterine cancer, besides of course in those cases of lymphoma, and leukemia

group of malignant tumours, where the therapy with cortisone and cortisone-like steroids is already used. In all these cases a rapid improvement is observed in the general conditions of the patient with an increase in appetite and a restoration of the vital forces. The effect of this treatment on pain is also notable; thus the quantity of morphine required can be appreciably reduced and, in some cases, may even not be necessary.

Although the liquid vehicle used in the compositions according to the invention has been defined in somewhat narrow terms, it should be understood that one may, if desired, add to the composition other pharmocological substances in addition to the adreno-cortical hormones. Substances of this nature include, for example sex hormones and products related to steroid hormones.

Moreover, one may add to the composition desired pharmaceutically acceptable adjuvants such as antioxidants and conserving or antiseptic agents (such as mono- or polyhydric phenols and ethers thereof) to assist the blending and prolong the stability of the components of the composition.

In order that the invention may be well understood, the following examples are given by way of illustration only.

EXAMPLE 1

Cortisone trimethylacetate (5 g.) was ground to a fine powder and suspended in a two litre mixture of glyceryl and ethyl ricinoleates. 5 mg/litre of propyl gallate and nordihydroguaiaretic acid (in equal parts) were added. The mixture was heated on a water-bath with occasional shaking of the suspension so as to obtain a clear and homogeneous solution. The resultant solution was then transferred into neutral glass 2 cc ampoules, each ampoule thus containing 5 mg. of cortisone trimethylacetate. The ampoules, sealed under nitrogen, were sterilised at a temperature of 120°C., for 30 minutes. A number of the ampoules were used for biological experiments. The remainder were maintained for some weeks in the ice-chest and then for some months at room temperature. The ampoules thus treated remained perfectly clear and homogeneous, even after many months had elapsed from the date of their preparation. The addition of small crystals of cortisone trimethylacetate failed to cause either opalescence or the formation of a crystalline precipitate.

The comparison of the biological activity of the oily solution of cortison trimethylacetate was carried out with an aqueous suspension of cortisone acetate at the same concentration (mg/cc), using the test of the survival of adrenalectomised rats treated with one single injection of the steroid. The test was carried out on male rats, 30 days old and weighing 60 gr each. Bilateral adrenalectomy was carried out under ether narcosis, according to the Grollman's technique. 3—4 hours after the adrenalectomy, the animals were subdivided into two groups of ten animals each. All the animals of one group were treated with one single injection of 2.5 mg of cortisone acetate in aqueous suspension. All the animals of the other group were treated with one single injection of 2.5 mg of cortisone trimethylacetate in oily solution. A third group of ten adrenalectomised animals served as controls. The results obtained are shown in the following table.

TABLE 3

Days after intervention	Number of living animals		
	Untreated	Treated with 2.5 mg of cortisone acetate in aqueous suspension	Treated with 2.5 mg of cortisone trimethylacetate in oily solution
5	2	10	10
6	0	8	10
7		8	10
8		8	10
9		4	10
10		4	10
11		4	10
12		2	7
13		0	7
14			6
15			3
16			2

EXAMPLE 2

Cortisone oenanthate (500 g., m.p. 138—140°C.), cortisone cyclopentylpropionate (300 g. m.p. 154—156°C.) and cortisone phenylpropionate (200 g., m.p. 173—175°C.) were suspended in a 20 litre mixture of glyceryl triricinoleate and ethyl oleate (1 : 1), containing nordihydroguaiaretic acid in the proportion of 10 mg/litre. The mixture was stirred mechanically, the internal temperature being kept at 100°C so as to obtain a clear and homogeneous solution. This solution was then introduced into 2 cc. ampoules, so that each one contained exactly 100 mg of the mixture of the cortisone esters (50 mg/cc). The ampoules, sealed under nitrogen, were sterilised at a temperature of 120°C for about 30 minutes. With the exception of some of these ampoules, which were used for biological experiments, the remainder were maintained for a few weeks, at about 0°C in an ice-chest, then for some months at room temperature. None of the ampoules thus treated showed any turbidity or precipitate even a few months after the date of their preparation.

EXAMPLE 3

A mixture of cortisone trimethylacetate (100 g., m.p. 260—262°C.), dehydrocorticosterone trimethylacetate (100 g., m.p. 186—187°C.) and desoxycorticosterone trimethylacetate (100 g., m.p. 200—202°C.) was dissolved at a temperature of about 80°C, in a 40 litre solution of ethyl ricinoleate diluted with 10% of ethyl oleate and containing, in the proportion of 8 mg/litre, nordihydroguaiaretic acid and propyl gallate in equal parts.

The clear solution was then introduced into 4000 containers of 10 cc. capacity so that each contained 75 mg of the active substances (7.5 mg/cc). This oily solution is very efficient in the treatment of Addisonians and in adrenocortical deficiencies.

EXAMPLE 4

Prednisone oenanthate (30 g., m.p. 176—178°C.) was admixed with 2.5 litres of a propylenyl ricinoleate solution containing propyl gallate in the proportion of 8 mg/litre in a 5-litre neutral glass flask. The flask was heated on a water-bath, the suspension being occasionally shaken and the temperature slowly raised until dissolution was complete. The clear and homogeneous solution thus obtained was introduced into 2 cc. ampoules so that each ampoule contained exactly 24 mg. of prednisone oenanthate. The ampoules were closed in a nitrogen atmosphere, sterilised and then maintained for some weeks in the ice-chest. The solution inside the ampoules remained quite clear and homogeneous and was practically uncongealable.

In the same way, prednisone cyclopentylpropionate (7.5 g., m.p. 188—190°C) were dissolved in 7.5 litres of a mixed solution of glyceryl and ethyl ricinoleates, to which had been added, in the proportion of 5 mg/litre, nordihydroguaiaretic acid. The solution thus obtained was introduced into 10 cc. containers. (Each container thus contained 100 mg of prednisone cyclopentylpropionate). A few months after the date of preparation the solution inside the containers was still perfectly homogeneous. There was no formation of any precipitate, even after the addition of seed crystals of prednisone cyclopentylpropionate.

In the same manner as above prednisone was dissolved in a mixture of glyceryl and ethyl ricinoleates (1:1). The biological activity of the prednisone, administered parenterally, in oily solution, was compared with that of prednisone administered orally. The comparison was carried out on albino rats and the action on thymus, adrenals and body weight was observed.

The liposoluble prednisone was administered in doses of 50—100—200—400γ and the orally administered prednisone in doses of 100—200—400—600—1000γ. This treatment was continued for five consecutive days; on the 6th day the animals were sacrificed; the adrenals and thymus were removed and weighed immediately. The results are shown in the table below.

TABLE 4

Treatment	Animals No.	Body weight change %	Adrenals weight mg	Thymus weight mg
Controls	31	107.7 ± 1.26	13.1 ± 0.36	89.4 ± 4.79
Prednisone i.m.				
400 × 5	12	85.2 ± 1.29	7.7 ± 0.21	16.1 ± 0.26
200 × 5	23	90.2 ± 2.92	8.9 ± 0.37	22.3 ± 1.17
100 × 5	12	103.8 ± 3.10	11.6 ± 0.60	36.9 ± 5.19
50 × 5	6	102.6 ± 2.92	13.1 ± 0.54	57.7 ± 6.08
Prednisone per os				
1000 × 5	6	106.1 ± 2.23	11.0 ± 0.81	23.1 ± 1.95
600 × 5	6	105.6 ± 2.50	13.0 ± 0.44	41.0 ± 2.59
400 × 5	12	108.4 ± 2.69	12.4 ± 0.56	43.2 ± 4.12
200 × 5	19	109.3 ± 1.44	12.8 ± 0.88	51.6 ± 3.74
100 × 5	6	104.8 ± 2.23	13.6 ± 0.89	50.0 ± 6.16

These results show that, with regard to the activity on thymus, adrenals and body weight, the prednisone preparation in oily solution administered intramuscularly is much more active than the orally administered prednisone.

EXAMPLE 5

Hydrocortisone acetate (15 g., m.p. 219—220°) was dissolved by heating in 1.5 litres of propylenyl ricinoleate, prepared by esterification of ricinoleic acid with propylene glycol. The solution (containing 10 mg of hydrocortisone acetate per cc) was introduced into 2 cc ampoules which were then sealed under vacuum and sterilized in an autoclave.

The ampoule solution was biologically tested —after diluting 1:10 with sesame oil—for its effects on the survival of adrenalectomised rats and it was found to be very effective.

EXAMPLE 6

Prednisolone (100 g., m.p. 240—242°C) was dissolved by heating in a mixture of ethyl ricinoleate and ethyl oleate (1:1) to give a concentration of 15 mg/cc. Multidose containers (10 cc.) were filled with this solution in the usual manner, sealed and sterilised.

This oily solution of prednisolone was used to treat a number of cases of malignant neoplasia. Tumours of the breast, tumours of the uterine portio and of the skin and primitive tumours of the bone were treated. Subjective

improvements were observed for two or three months. The patients reported a definite feeling of well-being, disappearance of pain, increase in appetite, and euphoria. The oily solution of prednisolone was well tolerated, well absorbed at the site of injection, and accompanied by no undesirable side-effects, even in cases where high doses were administered.

EXAMPLE 7

In the same manner as in Examples 1—6, oily solutions for use in parenteral administration were prepared with other steroids using glyceryl, propylenyl and ethyl ricinoleates singly and in admixture as the liquid vehicle.

Among the steroids made up into such preparations were 9α-fluoro derivatives of prednisone and prednisolone and their corresponding Δ^6-dehydro or 6-methyl derivatives, i.e.: 9α-fluoro - $\Delta^{1:4}$ - pregnadiene - 11β:17α:21-triol-3:20-dione; $\Delta^{1:4:6}$ - pregnatriene - 11β:17α:21 - triol - 3:20 - dione; 9α-fluoro-$\Delta^{1:4:6}$-pregnatriene - 11β:17α:21 - triol - 3:20-dione; 9α - fluoro - 6 - methyl - $\Delta^{1:4}$ - pregnadiene-11β:17α:21-triol-3:20-dione.

EXAMPLE 8

Prednisone trimethylacetate (8 g.) was ground to a fine powder and suspended in a two litre mixture of glyceryl and ethyl ricinoleates, 5 mg/litre of propyl gallate and nordihydroguaiaretic acid (in equal parts) were then added. The mixture was heated on a water-bath, the suspension being occasionally shaken and the temperature slowly raised until a clear and homogeneous solution was obtained. This solution was then transferred into neutral glass 2 cc ampoules, each ampoule thus having 8 mg. of prednisone trimethylacetate. The ampoules, sealed under nitrogen and sterilised, were maintained for some weeks in an ice-chest and then for some months at room temperature. The ampoules thus treated remained perfectly clear and homogeneous, even after many months had elapsed from the date of their preparation. Even the addition of small crystals of prednisone trimethylacetate caused neither opalescence nor crystalline precipitation.

The biological activity of prednisone trimethylacetate in the above vehicle was compared to that of the prednisone orally administered. On the turpentine granuloma test prednisone trimethylacetate in oily solution showed an antiinflammatory power clearly superior to that of the prednisone, administered by oral route.

EXAMPLE 9

Prednisone trimethylacetate (35 g., m.p. 274—278°C.), prednisone oenanthate (80 g., m.p. 176—178°C.) and prednisone cyclopentylpropionate (75 g., m.p. 188—190°C.) were suspended in a 10 litre mixture of glyceryl triricinoleate and ethyl oleate (1:1), containing nordihydroguaiaretic acid in the proportion of 10 mg/litre. The mixture was stirred mechanically, the internal temperature being kept at 100°C. so as to obtain a clear and homogeneous solution. This solution was then introduced into 2 cc. ampoules, so that each contained exactly 38 mg of the mixture of the prednisone esters (19 mg/cc.). The ampoules, sealed under nitrogen, were sterilised at a temperature of 120°C for about 30 minutes. After a few weeks at about 0°C. they were maintained for some months at room temperature. None of the ampoules thus-treated showed any turbidity or precipitate even a few months after the date of their preparation.

The oily solution of the prednisone esters was biologically tested—after a dilution 1:10 with sesame oil—for its effects on the survival of the adrenalectomised rats and it was found to be very effective.

EXAMPLE 10

A mixture of prednisone trimethylacetate (15 g.), prednisolone trimethylacetate (55 g.) and 9α-fluoro-prednisolone trimethylacetate (30 g.) was dissolved, at a temperature of about 80°C., in a 5 litre solution of ethyl ricinoleate containing 10% of ethyl oleate and nordihydroguaiaretic acid and propyl gallate, in equal parts, in the proportion of 8 mg/litre.

The clear solution was then introduced into 500 containers of 10 cc. each, so that each contained 200 mg. of the trimethylacetate mixture.

In the same manner, prednisone oenanthate (20 g.) and prednisolone oenanthate (80 g.) were dissolved in a 2 litre solution of glyceryl ricinoleate (50 mg/cc).

EXAMPLE 11

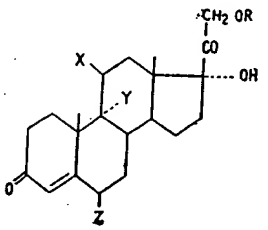
Prednisone (4 g.) and prednisolone (8 g.) were dissolved by heating in 500 cc. of propylenyl ricinoleate, prepared by the esterification of ricinoleic acid with propylene glycol. The solution thus prepared (containing 24 mg/cc of hormones mixture) was assayed on the spontaneous mammary tumour of mice. In several cases a temporary inhibition or retardation of the growth, and also hardening of the tumour was observed.

WHAT WE CLAIM IS:—

1. An oily composition adapted for parenteral administration comprising an adreno-cortical hormone as herein defined in solution in a liquid vehicle consisting of a parenterally acceptable ester of ricinoleic acid with a monohydric or polyhydric alcohol containing two or three carbon atoms per molecule with or without other parenterally acceptable compatible adjuvants which are not esters.

2. An oily composition as claimed in claim 1 in which said alcohol is ethyl alcohol, propylene glycol or glycerol.

3. An oily composition as claimed in claim 1 or 2 in which said adreno-cortical hormone is one having the general formula:—



where

X is ketonic oxygen or a hydroxyl group

Y is hydrogen or a halogen atom

Z is a hydrogen atom or a methyl group and

R is hydrogen or an acyl group or a Δ^1 or a $\Delta^{1:6}$-dehydro-derivative thereof.

4. An oily composition as claimed in any of the preceding claims in which a mixture of adreno-cortical hormones is used.

5. An oily composition as claimed in any of the preceding claims in which a mixture of said ricinoleic esters is used.

6. A modification of an oily composition as claimed in any of the preceding claims in which the liquid vehicle also contains a further ester component consisting of a parenterally acceptable ester of an alcohol with a carboxylic acid other than ricinoleic acid, said ester containing at least six carbon atoms per molecule.

7. An oily composition as claimed in claim 6 in which said ester is olive oil, sesame oil, ethyl oleate or benzyl benzoate.

8. A composition as claimed in any of the preceding claims in which pharmacologically active substances other than adreno-cortical hormones are present.

9. An oily composition as claimed in any of the preceding claims containing an antioxidant.

10. An oily composition as claimed in any of the preceding claims in which the adreno-cortical hormone is used in an amount of 0.1 to 5% by weight of the liquid vehicle.

11. An oily composition substantially as herein described with reference to any of the examples.

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